REVIEW ARTICLE

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Are All Statins the Same?

Focus on the Efficacy and Tolerability of Pitavastatin

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Abstract

Pitavastatin is the newest member of the HMG-CoA reductase inhibitor family and is approved as adjunctive therapy to diet to reduce elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein (Apo) B, and triglycerides and to increase levels of high-density lipoprotein (HDL) cholesterol in adult patients with primary hyperlipidemia or mixed dyslipidemia. Pitavastatin undergoes minimal metabolism by cytochrome P450 (CYP) enzymes and, therefore, has a low propensity for drug-drug interactions with drugs metabolized by CYP enzymes or the CYP3A4 substrate grapefruit juice. In clinical trials, pitavastatin potently and consistently reduced serum levels of total, LDL, and non-HDL cholesterol, and triglycerides in patients with primary hypercholesterolemia where diet and other non-pharmacological measures were inadequate. Mean reductions from baseline in serum total and LDL cholesterol and triglyceride levels were 21–32%, 30–45%, and 10–30%, respectively. Moreover, a consistent trend towards increased HDL cholesterol levels of 3–10% was seen. Long-term extension studies show that the beneficial effects of pitavastatin are maintained for up to 2 years. Pitavastatin produces reductions from baseline in serum total and LDL cholesterol levels to a similar extent to those seen with the potent agent atorvastatin and to a greater extent than those seen with simvastatin or pravastatin.

In the majority of other studies comparing pitavastatin and atorvastatin, no significant differences in the favorable effects on lipid parameters were seen, although pitavastatin was consistently associated with

trends towards increased HDL cholesterol levels. Pitavastatin also produces beneficial effects on lipids in patients with type 2 diabetes mellitus and metabolic syndrome without deleterious effects on markers of glucose metabolism, such as fasting blood glucose levels or proportion of glycosylated hemoglobin. Pitavastatin appears to exert a number of beneficial effects on patients at risk of cardiovascular events independent of lipid lowering. In the JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study, pitavastatin was non-inferior to atorvastatin at reducing plaque volume in patients with ACS undergoing percutaneous coronary intervention. Further beneficial effects, including favorable effects on the size and composition of atherosclerotic plaques, improvements in cardiovascular function, and improvements in markers of inflammation, oxidative stress, and renal function, have been demonstrated in a number of small studies. Pitavastatin is generally well tolerated in hyperlipidemic patients with or without type 2 diabetes, with the most common treatment-related adverse events being musculoskeletal or gastrointestinal in nature. Increases in plasma creatine kinase levels were seen in <5% of pitavastatin recipients and the incidence of myopathy or rhabdomyolysis was extremely low. In summary, pitavastatin, the latest addition to the statin family, produces potent and consistent beneficial effects on lipids, is well tolerated, and has a favorable pharmacokinetic profile. The combination of a potent decrease in total and LDL cholesterol levels and increase in HDL cholesterol levels suggest that pitavastatin may produce substantial cardiovascular protection.

Cardiovascular disease (CVD) is the leading cause of death in men and women in the majority of European countries, causing over 4.3 million deaths per year.[1] The WHO MONICA (Multinational Monitoring of Trends and Determinants in Caiovascular Disease) study showed great variation in the prevalence of cholesterol levels of ≥6.5 mmol/L, ranging from 8% to 53% in men and from 15% to 40% in women.[2] Mean serum cholesterol levels across Europe ranged from 4.5 to 6.5 mmol/L in men and from 4.5 to 6.2 mmol/L in women.[3] The INTERHEART study (A Study of Risk Factors for First Myocardial Infarction in 52 Countries) estimated that individuals with dyslipidemia are three times more likely to have a myocardial infarction than those with normal lipid levels, and that abnormal lipid levels are the cause of 45% of myocardial infarctions in Western Europe.[4]

The relationship between serum cholesterol levels and cardiovascular risk is well defined.[5] A 10% reduction in plasma total cholesterol levels is associated with a 25% reduction in the 5-year incidence of CVD, and a 1 mmol/L reduction in low-density lipoprotein (LDL) cholesterol level is associated with a 20% reduction in cardiovascular events.[6] A strong relationship also exists between low high-density lipoprotein (HDL) cholesterol levels and cardiovascular risk, whereas a high triglyceride level indicates the need to investigate the cluster of risk factors termed 'metabolic syndrome.'[5]

HMG-CoA reductase inhibitors (statins) are the drugs of choice in patients with dyslipidemia.[5] In addition to reducing hyperlipidemia, this class of agents has been shown to reduce cardiovascular events, mortality, and the need for coronary revascularization.[5] Furthermore, intensive statin therapy appears to halt progression or induce regression of coronary atherosclerosis[7,8] and further reduce the incidence of major vascular events.[9]

Pitavastatin is the newest member of the HMG-CoA reductase inhibitor class of agents and is approved as adjunctive therapy to diet to reduce elevated levels of total cholesterol, LDL cholesterol, apolipoprotein (Apo) B, and triglycerides, and to increase HDL cholesterol levels in adult patients with primary hyperlipidemia or mixed dyslipidemia.[10] This review discusses the pharmacology, efficacy, and tolerability of pitavastatin in these indications. Data were identified using a search performed on MEDLINE, and clinical trials of pitavastatin in humans published between 1 January 2000 and 19 October 2010 were included. Additional data are also discussed at the discretion of the author.

1. Pharmacodynamic Profile

1.1 Mechanism of Action

Pitavastatin is a synthetic statin that competitively inhibits HMG-CoA reductase, thereby inhibiting hepatic cholesterol synthesis and improving lipid profiles.[10] The drug inhibits HMG-CoA reductase with a 50% inhibitory concentration (IC_{50}) of 6.8 nmol/L, which is 2.4-fold higher than that observed with simvastatin and approximately 6.8-fold higher than that observed with pravastatin.[11] Inhibition of cholesterol synthesis from radiolabeled acetic acid in cultured human hepatoma cells

by pitavastatin occurred with an IC_{50} of 5.8 nmol/L, which is 2.9- and 5.7-fold higher than that observed with simvastatin and atorvastatin, respectively.[12] Inhibition of sterol synthesis in rat liver occurred with a dose that produces a 50% effective response (ED_{50}) of 0.13 mg/kg and is three times stronger than simvastatin in the same animal.[13]

Induction of LDL receptor messenger RNA (mRNA) by statins may reduce plasma LDL cholesterol levels. In *in vitro* studies pitavastatin has been shown to increase LDL receptor mRNA,[12] LDL binding to the LDL receptor and internalization into the cells,[14] and degradation of Apo B.[15] Relative to atorvastatin and simvastatin, pitavastatin also showed greater induction of LDL cholesterol receptor expression[12] and superior Apo AI secretion-promoting effects.[16]

1.2 Other Effects

Recent evidence suggests that statins may have beneficial effects on vascular function over and above those produced by cholesterol lowering alone, often termed 'pleiotropic' effects, and *in vitro* and *in vivo* studies suggest that pitavastatin also exhibits these effects. Anti-inflammatory effects observed with pitavastatin in *in vitro* studies include inhibition of C-reactive protein (CRP)-induced interleukin-8 production by endothelial cells,[17] stimulation of monocyte chemoattractant protein-1,[18] and inhibition of the expression of pentraxin 3 (PTX3).[19] Pitavastatin inhibits plasminogen activator inhibitor-1 (PAI-1) and tissue factor,[20,21] and induces tissue plasminogen activator and thrombomodulin,[20-22] processes that are likely to exert beneficial effects on atherothrombotic events. In a rabbit model of hyperlipidemia, pitavastatin 0.5 mg/kg/day administered for 16 weeks was associated with a reduction in the progression of aortic atherosclerosis.[23] Pitavastatin improved the composition of vulnerable plaques to assist plaque stabilization by increasing collagen deposition and decreasing macrophage infiltration.[23] Pitavastatin has been shown to reduce the generation of reactive oxygen species,[24] improve endothelial function,[25] increase nitric oxide production,[26] inhibit cell adhesion,[18] attenuate smooth muscle cell contraction,[27] enhance angiogenesis,[28] and promote Apo AI production.[16] Even at low doses, pitavastatin inhibited human coronary artery smooth muscle cell proliferation to a greater extent than atorvastatin, simvastatin, fluvastatin, rosuvastatin, and pravastatin.[29] In *in vitro* studies, pitavastatin inhibited adipocyte differentiation via inhibition of peroxisome proliferator-activated receptor-γ expression and activation of preadipocyte factor-1.[30]

2. Pharmacokinetic Profile

2.1 Absorption and Distribution

In humans, pitavastatin achieves maximum plasma concentrations (C_{max}) about 1 hour after oral administration, with an absorption rate of 80% and an absolute bioavailability of pitavastatin oral solution of 51% (administration with a fat meal decreases C_{max}, but does not affect the pitavastatin area under the plasma concentration-time curve [AUC]).[31] Pitavastatin is selectively distributed to the liver, with drug concentrations in rat liver shown to be 54-fold higher than those seen in plasma.[32] There are no clinically relevant effects of food on the pharmacokinetic profile of pitavastatin.[33]

2.2 Metabolism and Excretion

Pitavastatin undergoes minimal cytochrome P450 (CYP) metabolism in the liver; the drug enters the enterohepatic circulation, which in turn prolongs its elimination half-life ($t_{½}$) to approximately 11–12 hours.[32-34] Since pitavastatin is minimally metabolized by the CYP isoenzymes, it has a low propensity for drug-drug interactions and shows minimal interaction with grapefruit juice (a CYP3A4 substrate).[35,36] However, caution and/or dose reductions are recommended when pitavastatin is co-administered with erythromycin (which results in a 2.8-fold increase in pitavastatin AUC and a 3.6-fold increase in C_{max}), lopinavir/ritonavir, rifampicin (rifampin), fibric acid derivatives (e.g., fenofibric acid, gemfibrozil), niacin, and warfarin.[10]

Like other statins, the uptake of pitavastatin in the liver is understood to be mediated by the organic anion transporter protein (OATP) 2;[37,38] thus, exposure to pitavastatin is increased when it is co-administered with OATP2 inhibitors. When cyclosporine, an OATP1B1 inhibitor, was co-administered with pitavastatin, a 5-fold increase in the pitavastatin AUC from time zero to 24 hours (AUC_{24}) was observed.[39] OATP1B1, which is encoded by the *SLCOB1* gene, is also involved in the uptake of pitavastatin in the liver. Various pharmacokinetic studies have shown that single nucleotide polymorphisms in this gene significantly alter the pharmacokinetics of pitavastatin in healthy volunteers.[40-44]

2.3 Special Patient Populations

Patients with mild to moderate hepatic impairment experience an increase in the plasma concentration of, and exposure to, pitavastatin. In patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, the pitavastatin

C_{max} was 1.2-fold and 2.5-fold, respectively, greater than observed in healthy volunteers; the respective values for AUC extrapolated to infinity (AUC_{∞}) were 1.3-fold and 3.5-fold higher.[45] In healthy volunteers and patients with mild or moderate hepatic impairment, mean pitavastatin $t_{½}$ values were 10, 9, and 14 hours, respectively.[45]

Patients with renal impairment also experience marked increases in pitavastatin exposure. The AUC_{∞} was 79% and 86% higher than that seen in healthy volunteers and in patients with moderate renal impairment (glomerular filtration rate [GFR] 30–59 mL/min/1.73 m^2) and end-stage renal disease undergoing hemodialysis, respectively.[10] The effect of mild or severe renal impairment on pitavastatin pharmacokinetics has not been studied.

There were no clinically significant differences in the pharmacokinetic profile of pitavastatin between elderly and non-elderly individuals.[46] The pitavastatin C_{max} and AUC were 10% and 30%, respectively, higher in young compared with old (aged ≥65 years) healthy volunteers.[10]

3. Lipid-Lowering Effects

3.1 In Patients with Dyslipidemia

The lipid-lowering effect of pitavastatin in patients with dyslipidemia has been investigated in nine large studies of between 8 and 52 weeks' duration (table I).[47-55] The majority were randomized, open-label, multicenter studies. However, three studies were double-blind,[47,50,52] one study contained a single arm,[48] and one study was performed at a single center.[53] Three long-term follow-up studies[58-60] and one post-marketing surveillance study[61,62] are also available. Patients in the studies had primary hypercholesterolemia,[47-54] hyperlipidemia,[55] or combined dyslipidemia.[47,50] Patients received pitavastatin 1–4 mg daily and efficacy was compared with pravastatin 10 mg daily,[52] simvastatin 10–20 mg daily,[50,51] and atorvastatin 10–20 mg daily.[47,49,53-55] Where stated, the primary endpoints of studies were change from baseline in multiple lipid parameters (total cholesterol, LDL cholesterol, and triglyceride levels),[52] LDL cholesterol levels,[47,50,51] or non-HDL cholesterol levels,[54] or the proportion of patients achieving the LDL cholesterol goal.[49] The lipid-lowering effects of pitavastatin have also been reported in small studies or as a secondary endpoint in studies, but these will not be discussed further in this section.[63-69]

Pitavastatin consistently produces significant reductions from baseline in serum levels of total, LDL, and non-HDL cholesterol. In trials of up to 52 weeks' duration, pitavastatin decreased total cholesterol levels by 21.0–32.4% and LDL cholesterol levels by 30.3–44.6% compared with baseline levels (table I).[47-55] Where measured, pitavastatin was associated with reductions from baseline in non-HDL cholesterol levels of 34.7–41.1%.[47,50,54] LDL cholesterol target levels were achieved by 56.8–93.9% of individuals when using National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria[47,49-51,53] and 56.8–78.5% using European Atherosclerosis Society (EAS) criteria.[47,50]

Pitavastatin also produces significant reductions from baseline in serum triglyceride levels and a trend towards increased HDL cholesterol levels. In studies, pitavastatin reduced serum triglyceride levels by 9.9–29.8%[47,49-55] and increased serum HDL cholesterol levels by 2.6–8.9%,[47-55] although the changes were not always statistically significant (table I). Pitavastatin is associated with favorable effects on a number of other lipid parameters, including significant increases from baseline in Apo AI (5.6–7.2%)[47,50,52] and Apo AII (4.2%) levels,[52] and significant decreases in the levels of Apo B (–29.7% to –35.3),[47,50,52] Apo CII (–15.7%),[52] Apo CIII (–9.5%),[52] Apo E (–22.9%),[52] oxidized LDL (–22.3% and –25.5%, with pitavastatin 2 mg and 4 mg, respectively),[47] and remnant-like particle (RLP) cholesterol (–22.8%).[48]

Long-term extension studies of clinical trials show that pitavastatin is efficacious for up to 2 years' duration.[59,60] In an open-label extension to the study by Ose et al.[60] in which patients who had previously received pitavastatin, atorvastatin, or simvastatin received pitavastatin 4 mg daily, the proportion of patients achieving NCEP and EAS LDL cholesterol targets at 52 weeks was 74.0% and 73.5%, respectively. An extension to a small open-label study showed that decreases in levels of total and LDL cholesterol and triglycerides were stable over 104 weeks. Reductions in other lipid parameters, such as Apo B levels, were also maintained.[59]

Pitavastatin produces similar improvements in lipid parameters to commonly used statins. Reductions from baseline in serum LDL, total, or non-HDL cholesterol and triglyceride levels were generally similar to those seen with equivalent doses of atorvastatin (table I).[47,49,53-55] For example, similar reductions from baseline in serum LDL cholesterol levels were seen in patients receiving daily doses of pitavastatin 2 mg and atorvastatin 10 mg, and pitavastatin 4 mg and atorvastatin 20 mg, with non-inferiority demonstrated between the comparators (figure 1a). Moreover, there was no significant difference between comparators in the reduction of other lipid parameters and the proportion of patients achieving lipid target levels (figure 1a and b). However, in two trials, atorvastatin produced significantly greater reductions from baseline in levels of triglycerides (–21% vs –11%; $p < 0.05$),[55] total cholesterol

Table I. Effect of pitavastatin on lipid parameters in patients with primary hypercholesterolemia, hyperlipidemia, or combined dyslipidemia in clinical studies of up to 52 weeks' duration[47-55]

Study and year (design; duration)	No. of patients	Drug and dose (mg/day)	Changes in lipid levels from baseline values (%)					Patients achieving LDL-C goal (%)
			LDL-C	HDL-C	non-HDL-C	TC	TG	
Saito et al. 2002[52] (r, db, mc; 12 wk)	125	PIT 2	–37.6**†	+8.9	NR	–28.0**†	–23.3*†	75[a]
	111	PRA 10	–18.4**	+9.8	NR	–13.8**	–20.2*	36[a]
Park et al. 2005[51] (r, op, mc; 8 wk)	49	PIT 2	–38.2	+8.3	NR	–26.9	–29.8	93.9[b]
	46	SIM 10	–39.4	+3.6	NR	–28.5	–17.4	91.3[b]
Yoshitomi et al. 2006[55] (op, mc; 12 wk)	70	PIT 1	–38*	+3	NR	–28*	–11	NR
	67	ATO 10	–41*	+7*	NR	–29*	–21*†	NR
Lee et al. 2007[49] (r, op, mc; 8 wk)	110	PIT 2	–42.9	+7.1	NR	–28.2	–9.9	92.7[b]
	112	ATO 10	–44.1	+6.7	NR	–29.6	–11.0	92.0[b]
Koshiyama et al. 2008[48] (mc; 52 wk)	178	PIT 1–2	–30.3[c]	+2.6[c]	NR	–21.0[c]	NR	NR
Yokote et al. 2008[54] (r, op, mc; 12 wk)	101	PIT 2	–42.6***	+3.2*	–39.0***#	–29.7***	–17.3***	NR
	103	ATO 10	–44.1***	+1.7	–40.3***	–31.1***	–10.7**	NR
Budinski et al. 2009[47] (r, db, mc; 12 wk)	316	PIT 2	–37.9##	+4.0	–34.7	–27.7	–14.1	56.8[b]/56.8[d]
	300	PIT 4	–44.6##	+5.0	–41.1	–32.4	–19.0	77.9[b]/78.5[d]
	102	ATO 10	–37.8	+3.0	–35.2	–28.1	–17.7	65.7[b]/59.8[d]
	103	ATO 20	–43.5	+2.5	–40.6	–32.7	–22.3	70.6[b]/76.5[d]
Ose et al. 2009[50] (r, db, mc; 12 wk)	315	PIT 2	–39.0††###	+6.0	–35.8††	–27.9††	–15.9	70.0[b]/59.6[d]
	323	PIT 4	–44.0###	+6.2	–40.5	–31.5	–16.8	79.6[b]/75.2[d]
	108	SIM 20	–35.0	+5.5	–32.3	–25.4	–15.6	64.5[b]/48.6[d]
	111	SIM 40	–42.8	+6.8	–39.4	–30.5	–16.1	78.2[b]/75.5[d]
Sansanayudh et al. 2010[53] (r, op, sc; 8 wk)	50	PIT 1	–37.4***	+2.8	NR	–27.6***	–10.4***	74.0[b]
	50	ATO 10	–45.8***†	–0.4	NR	–32.3***†	–7.1***	84.0[b]

a Serum LDL-C level <140 mg/dL.

b National Cholesterol Education Program Adult Treatment Panel III criteria.[56]

c Significant change vs baseline, p-value not stated.

d European Atherosclerosis Society criteria.[57]

ATO = atorvastatin; **db** = double-blind; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **mc** = multicenter; **NR** = not reported; **op** = open-label; **PIT** = pitavastatin; **PRA** = pravastatin; **r** = randomized; **sc** = single-center; **SIM** = simvastatin; **TC** = total cholesterol; **TG** = triglycerides; **wk** = weeks; * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs baseline; † $p<0.05$ vs comparator; †† $p<0.05$ vs SIM 20; # non-inferiority to ATO 10 demonstrated; ## PIT 2 demonstrated non-inferiority to ATO 10; PIT 4 demonstrated non-inferiority to ATO 20; ### PIT 4 demonstrated equivalence to SIM 40.

(–32.3% vs –27.6%; $p=0.005$),[53] and LDL cholesterol (–45.8% vs –37.4%; $p<0.001$).[53] Reductions from baseline in serum lipid levels with pitavastatin were generally greater than those seen with simvastatin or pravastatin.[50-52] For example, in the trial by Ose et al.,[50] pitavastatin 2 mg daily was associated with a significantly greater reduction from baseline in total (–27.9% vs –25.4%), LDL (–39.0% vs –35.0%), and non-HDL (–35.8% vs –32.3%) cholesterol levels compared with simvastatin 20 mg daily (all $p<0.05$). Pitavastatin 2 mg daily produced significantly greater reductions from baseline in LDL (–37.6% vs –18.4%) and total (–28.0% vs –13.8%) cholesterol and triglyceride (–23.3% vs 20.2%) levels compared with pravastatin 10 mg daily in a 12-week study (all $p<0.05$).[52]

The LIVES (Livalo Effectiveness and Safety) study was a 2-year, single-arm, uncontrolled, observational, post-marketing study conducted in almost 21 000 patients with hypercholesterolemia or familial hypercholesterolemia designed to assess the safety and efficacy of pitavastatin in the 'real-world' setting.[61] A significant reduction from baseline in the level of LDL cholesterol (112.5 vs 164.8 mg/dL; $p<0.001$) was seen, and 66.5–88.2% of primary prevention and 50.3% of secondary prevention patients achieved Japan Atherosclerosis Society

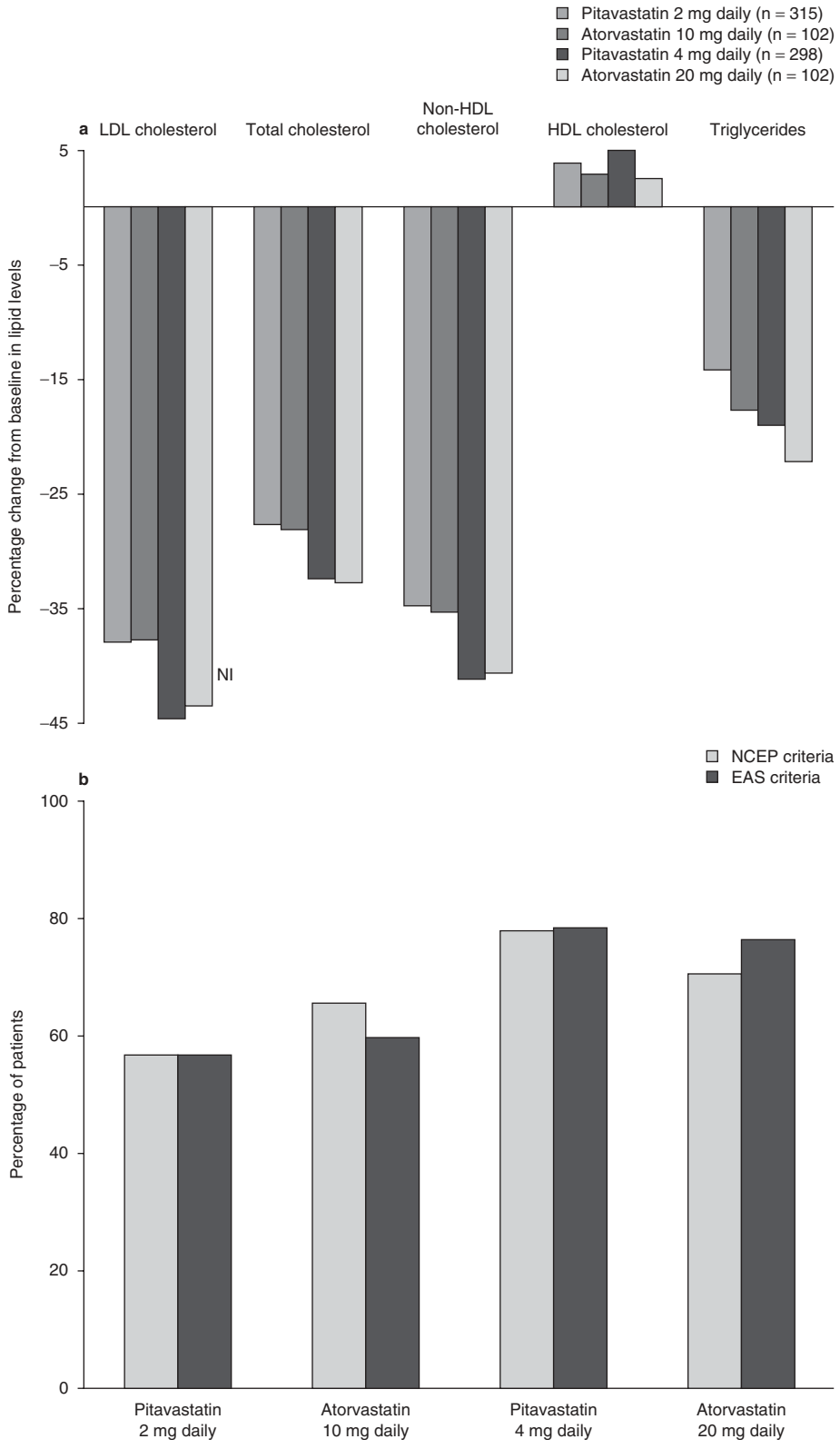

Fig. 1. Effect of pitavastatin or atorvastatin on (**a**) lipid parameters and (**b**) the proportion of patients achieving target lipid levels according to National Cholesterol Education Program (NCEP) or European Atherosclerosis Society (EAS) criteria in a prospective, randomized, double-blind, multicenter study in patients with primary hypercholesterolemia or combined dyslipidemia.[47] **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **NI** = non-inferiority demonstrated.

guideline-recommended LDL cholesterol targets.[61] A significant reduction in triglyceride level (139.7 vs 165.8 mg/dL; $p < 0.001$) and increase in HDL cholesterol level (60.5 vs 59.5 mg/dL; $p < 0.001$) was also reported.[61]

3.2 In Diabetic Patients

The efficacy of pitavastatin in patients with type 2 diabetes mellitus has been studied in nine clinical trials of up to 52 weeks' duration (table II).[70-79] The trials were generally open-label and performed at a single center; one study was crossover in design,[72] two were randomized,[72,75] and one was a retrospective analysis.[78] Patients had type 2 diabetes or glucose intolerance and hyperlipidemia.

Pitavastatin produced significant reductions from baseline in total and LDL cholesterol, and triglyceride levels in patients with type 2 diabetes (table II). Reductions from baseline in serum LDL cholesterol levels were between –17.5% and –41.1%[70-78] and for total cholesterol levels were between –12.1% and –27.1%.[70,73,74,76,78] In one study, pitavastatin was associated with a 31.1% decrease in serum non-HDL cholesterol levels.[75] Pitavastatin also produced decreases in triglyceride levels of between –6.2% and –28.7%.[71,73-78] Increases from baseline in plasma HDL cholesterol levels were also seen in the majority of trials and ranged from +1.7% to +12.5%.[71-78]

The efficacy of pitavastatin (n = 28) was compared with atorvastatin (n = 25) in a small subgroup of patients with metabolic syndrome.[54] The change from baseline in LDL cholesterol levels was significantly greater in patients receiving pitavastatin compared with atorvastatin recipients (–45.8% vs –39.1%; $p = 0.0495$), although total cholesterol and non-HDL cholesterol levels were reduced to a similar extent. Pitavastatin

Table II. Effect of pitavastatin on lipid and blood glucose parameters in patients with type 2 diabetes mellitus or glucose intolerance in clinical studies of up to 52 weeks' duration[70-79]

Study and year (design; duration)	No. of patients	Drug and dose (mg/day)	Change in blood glucose parameters from baseline values (%)		Changes in lipid levels from baseline values (%)			
			fasting plasma glucose	HbA_{1c}	LDL-C	HDL-C	TC	TG
Sone et al. 2002[76] (mc; 8 wk)	33	PIT 2	+6.3	NR	–36.1***	+9.7*	–25.2***	–28.7*
Kawai et al. 2005[71] (mc; 8 wk)	79	PIT 1–2	+0.9	+0.3	–36.9***	+3.1	NR	–9.9***
Inami et al. 2007[70] (sc; 6 mo)	65 non-diabetic	PIT 2	NR	NR	–39.9***	NR	–28.7***	NR
	52 diabetic	PIT 2	NR	NR	–36.4***	NR	–26.3***	NR
Tokuno et al. 2007[77] (op, sc; 3 mo)	NR	PIT 1	+8.4	0.0	–26.9***	+1.7	NR	–22.3*
	NR	FEN 100	–11.9	0.0	–2.2	+12.2**	NR	–49.1***
Monden et al. 2008[72] (r, op, co, sc; 12 wk)	20	PIT 2	NR	NR	–33	+4.1	NR	NR
	20	ROS 2.5	NR	NR	–42††	+7.7	NR	NR
Sasaki et al. 2008[75] (r, op, mc; 52 wk)	88	PIT 2	+3.8	+5.5	–33.0	+8.2†	NR	–7.1
	85	ATO 10	+9.8	+3.9	–40.1††	+2.9	NR	–14.6
Yamakawa et al. 2008[78] (ret, mc; 3 mo)	95	PIT 2	–3.0	–1.4	–17.5	+1.8	–12.0***	–11.7
	99	ATO 10	+6.0	+5.7***	–28.4***	+1.8	–21.3***	–17.9
	85	PRA (NR)	NR	0.0	–16.1***	+3.6	–10.6***	–1.4
Motomura et al. 2009[73] (op, mc; 6 mo)	65	PIT 2	+1.5	+4.4	–41.1***	+4.5*	–27.1***	–6.2*
Nomura et al. 2009[74] (r, op, sc; 6 mo)	64	PIT 2	NR	0.0	–36.1***¥	+12.5**	–24.0***¥	–13.6*
	55	EPA 1800	NR	0.0	–10.9**	+4.7	–11.8**	–19.0***#
	72	PIT 2 + EPA 1800	NR	–3.1	–39.1***¥	+15.2***	–27.1***¥	–28.6***#

ATO = atorvastatin; **co** = crossover; **EPA** = eicosapentaenoic acid; **FEN** = fenofibrate; **HbA_{1c}** = proportion of glycosylated hemoglobin; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **mc** = multicentre; **NR** = not reported; **op** = open-label; **PIT** = pitavastatin; **PRA** = pravastatin; **r** = randomized; **ret** = retrospective; **ROS** = rosuvastatin; **sc** = single centre; **TC** = total cholesterol; **TG** = triglycerides; **wk** = weeks; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs baseline; † $p < 0.05$, †† $p < 0.01$ vs comparator; # $p < 0.05$ vs PIT; ¥ $p < 0.05$ vs EPA.

was associated with significant reductions in serum triglyceride levels and increases in HDL cholesterol levels from baseline, whereas atorvastatin was not.[54]

Pitavastatin also produced favorable effects on other lipid parameters, including reductions in the levels of RLP cholesterol (–30.9%; $p < 0.001$),[76] Apo B (–23.5% and –28.2%),[75,77] Apo E (–17.8%),[75] small dense LDL cholesterol (–32.4%; $p < 0.0001$),[77] large buoyant LDL cholesterol (–26.1%; $p < 0.0001$),[77] and increases in adiponectin (+28.4%; $p < 0.001$)[70] and Apo A1 (+4.9% and +5.1%)[75,77] levels compared with baseline. In one study, serum adiponectin levels remained unchanged at study end.[72] A significant increase in mean LDL size and LDL1 subfraction plus a decrease in LDL4 subfraction was seen in another study.[76]

Importantly, pitavastatin did not affect glycemic control. Although increases from baseline in fasting plasma glucose levels and the proportion of glycosylated hemoglobin (HbA_{1c}) were seen in the majority of studies, these changes were small and generally not statistically significant (table II).[71,73-78] Alterations in antihyperglycemic agents were generally not permitted during the study period.

3.3 In Other Patient Groups

Pitavastatin produces favorable effects on lipid levels in elderly patients and those with chronic kidney disease (CKD). In a study reported as an abstract, 962 elderly patients (aged ≥65 years) with primary hypercholesterolemia or combined dyslipidemia were randomized to treatment with pitavastatin 1, 2, or 4 mg daily or pravastatin 10, 20, or 40 mg daily for 12 weeks followed by pitavastatin 2 mg daily titrated to 4 mg daily after 8 weeks and continued for 60 weeks.[80] In the randomized phase, patients receiving pitavastatin experienced reductions in LDL cholesterol levels of 31–44% compared with 22–34% seen in pravastatin recipients.[80] The NCEP LDL cholesterol target was achieved in 83–91% of pitavastatin and 65–88% of pravastatin recipients. After patients entered the pitavastatin phase, 92% achieved NCEP targets after 8 weeks, and at 60 weeks, 99% and 70% of patients receiving pitavastatin 2 mg or 4 mg daily achieved the NCEP target, respectively.[80] The overall reduction in triglycerides levels was 20% and the level of HDL cholesterol rose by 9.6%.

In a small study in Japanese patients with dyslipidemia and stage I or II CKD, pitavastatin 2 mg daily led to significant reductions from baseline in levels of total (–27.9%) and LDL (–39.8%) cholesterol and triglycerides (–12.6%), plus an increase in HDL cholesterol levels (+5.6%) [all $p < 0.001$ vs baseline].[81] The addition of the cholesterol absorption inhibitor ezetimibe further enhanced the lipid-lowering efficacy of pitavastatin, suggesting a potential future combination strategy. The reductions from baseline in total (–36.7%) and LDL (–51.0%) cholesterol and triglyceride (–20.9%) levels were all significantly greater than those seen with pitavastatin monotherapy (all $p < 0.05$).[81]

4. Other Effects

4.1 Effect on Atherosclerosis

Pitavastatin significantly improved atherosclerosis compared with dietary and lifestyle advice in patients with hypercholesterolemia in small trials of 6–7 months' duration.[82,83] In one study, 32 patients with hypercholesterolemia and atrial fibrillation undergoing transesophageal echocardiography were randomized to treatment with pitavastatin 1–2 mg daily or diet.[82] Patients in the diet group received nutritional and lifestyle advice; both groups were reassessed after 7 months. Pitavastatin was associated with significantly greater reductions in levels of total and LDL cholesterol and triglycerides compared with the diet group.[82] Moreover, patients receiving pitavastatin experienced a significantly greater reduction in corrected integrated backscatter (c-IBS) and intimal media thickness (IMT) of the arterial media (–12.9% vs +8.7% and –11.7% vs +6.3%, respectively; both $p < 0.001$). In the intimal plaque, pitavastatin recipients experienced a significantly greater increase in c-IBS (+32.4 vs +19.0%; $p < 0.01$) and decrease in IMT (–10.8% vs +8.3%; $p < 0.001$) compared with patients receiving diet alone. In a second study, 82 patients undergoing intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) were retrospectively assigned to a low-fat diet plus pitavastatin 2 mg daily administered within 48 hours of PCI group or a low-fat diet alone group.[83] The group that received pitavastatin had significantly greater reductions in total and LDL cholesterol levels compared with the diet alone group. Plaque volume index (PVI) was significantly reduced in patients receiving pitavastatin compared with the diet group (–10.6% vs +8.1%; $p < 0.001$).[83] Furthermore, reductions in PVI correlated significantly with the follow-up ($r = 0.500$) and change in LDL cholesterol level ($r = 0.0479$) [both $p < 0.001$].

Regression of coronary plaque volume with pitavastatin was similar to that seen with atorvastatin in patients with ACS.[84,85] In the multicenter, randomized JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study, 307 patients with ACS undergoing IVUS-guided PCI were treated with pitavastatin 4 mg daily or atorvastatin 20 mg daily for between 8 and 12 months.[84] A similar

mean percentage decrease in plaque volume in patients receiving pitavastatin or atorvastatin was seen (−16.9% vs −18.1%; p = 0.05 compared with baseline for both with no significant difference between groups), demonstrating non-inferiority between the two drugs.[84] A smaller short-term study comparing the two drugs suggested that pitavastatin may be more effective in reducing fibrofatty plaque composition.[85]

4.2 Effect on Inflammation and Oxidative Stress

Pitavastatin was associated with significant reductions from baseline in levels of high-sensitivity CRP (hs-CRP) in patients with primary hypercholesterolemia or combined dyslipidemia with or without type 2 diabetes or ACS in studies of up to 12 months' duration.[48-50,68,72,73,84,86,87] In a study by Motomura et al.,[73] 65 Japanese patients with type 2 diabetes and serum LDL cholesterol levels ≥120 mg/dL, triglyceride levels <400 mg/dL, and HbA_{1c} <9.0% were treated with pitavastatin 2 mg daily for 6 months. hs-CRP levels were significantly reduced from baseline at 6 months and although they correlated significantly with age, they were not associated with changes in lipid parameters.[73]

Mixed findings with regard to hs-CRP levels have been observed in comparative trials with other statins. Pitavastatin 2 mg or 4 mg daily was associated with similar reductions in hs-CRP levels to simvastatin 20 mg or 40 mg daily in a 12-week study in patients with hypercholesterolemia or mixed dyslipidemia.[60] hs-CRP levels reduced to a similar extent in patients with hypercholesterolemia receiving pitavastatin 2 mg daily or atorvastatin 10 mg daily in a second study.[49] However, rosuvastatin 2.5 mg daily produced significant reductions in hs-CRP levels from baseline in patients with type 2 diabetes whereas pitavastatin 2 mg daily did not.[72]

In a number of small studies, pitavastatin has been associated with significant reductions from baseline in serum levels of tumor-necrosis factor-α in patients with ACS,[87] PAI-1 in patients with type 2 diabetes,[72] PTX3,[68] and matrix metalloproteinases 2 and 3[59] in patients with hypercholesterolemia. Pitavastatin also produced beneficial effects on markers of bone turnover, including calcium and *N*-terminal telopeptide of type I collagen in a 3-month study.[65] A number of markers of oxidative stress have shown significant improvement with pitavastatin treatment, including lectin-like oxidized LDL cholesterol ligands,[66] 8-hydroxy-2′-deoxyguanosine (8-OHdG),[81,88,89] and malondialdehyde-modified (MDA) LDL.[88]

4.3 Effect on Cardiovascular Function

Pitavastatin has been associated with improvements in cardiac function in a number of small controlled[67,69,90] and uncontrolled[68,88,91,92] studies of up to 12 months' duration in patients with hyperlipidemia, type 2 diabetes, heart disease, or heart failure and in smokers. In patients with stable heart disease and serum total cholesterol levels ≥220 mg/dL, pitavastatin was associated with a significant decrease in plasma brain natriuretic peptide levels (65.0 vs 83.1 pg/mL; p < 0.05) and a significant increase in echocardiographically assessed E/A wave velocity ratio (0.790 vs 0.741; p < 0.05) from baseline, whereas no significant changes were seen in controls.[92] A significant increase in left ventricular ejection fraction (42% vs 48%; p = 0.002) and decrease in left ventricular end-systolic volume (43 vs 40 mm^3; p < 0.001) from baseline was seen in patients with ischemic or non-ischemic heart disease treated with pitavastatin for a mean of 7.5 months.[91] In this study, left ventricular end-diastolic dimension and E/A wave velocity ratio did not alter significantly from baseline.

Pitavastatin improved arterial stiffness in two studies.[67,68] In patients with hypercholesterolemia and preserved left ventricular ejection fraction, pitavastatin was associated with reduced carotid arterial stiffness and improved ventricular systolic and diastolic function compared with no statin.[67] At endpoint, stiffness of the common carotid artery[1] was significantly lower in patients receiving pitavastatin (stiffness β of 4.1 vs 5.6; p < 0.05), whereas this parameter did not alter significantly in controls (5.1 vs 5.0). In an uncontrolled study, pitavastatin improved arterial stiffness in atherosclerotic patients, as well as reducing elevated PTX3 levels.[68] Pitavastatin produced short-term improvements in endothelial function in two studies.[69,90] Flow-mediated dilation was significantly greater in patients with hypercholesterolemia treated with pitavastatin 2 mg daily compared with atorvastatin 10 mg daily recipients (11.5% vs 8.6%; p < 0.001).[69] Moreover, pitavastatin was associated with the restoration of endothelial function in chronic smokers.[90]

A study in 45 patients with type 2 diabetes showed pitavastatin to be associated with a significant reduction in cardio-ankle vascular index, as well as significant reductions from baseline in 8-OHdG and serum MDA LDL.[88]

4.4 Effect on Renal Function

Pitavastatin reduced clinical markers of CKD in small studies in patients with non-diabetic CKD, with or without

1 Evaluated by M-mode ultrasonography and determined by the stiffness index, namely, stiffness β. Stiffness $\beta = \ln(SBP/DBP)/[(Ds-Dd)/Dd]$ where Ds and Dd are the end-systolic and end-diastolic diameters of the common carotid artery, respectively, and SBP and DBP are the systolic and diastolic BP, respectively. Stiffness βs are expressed as means of both common carotid artery measurements.

hyperlipidemia, or early diabetic nephropathy.[81,89,93] In two studies, pitavastatin 1 mg daily administered for 6 and 12 months was associated with significant reductions in urinary liver-type fatty acid-binding protein (L-FABP) levels and urinary albumin excretion.[89,93] While pitavastatin did not significantly reduce serum total cholesterol levels, significant reductions from baseline in urinary albumin excretion (58 vs 110 μg/min; $p < 0.01$) and urinary L-FABP levels (8.8 vs 18.6 μg/g creatinine; $p < 0.01$) were seen in diabetic patients with microalbuminuria (20–200 μg/min) receiving pitavastatin but not in placebo recipients.[89] The effects of pitavastatin on renal function in diabetic patients with macroalbuminuria and normal renal function or in patients with chronic renal failure who were also recruited in this study were not reported.[89] In non-diabetic patients with mild (stage I) CKD (mean serum creatinine level 1.0 mg/dL) and normal lipid levels, pitavastatin 1 mg daily administered for 6 months reduced urinary protein excretion (1.0 vs 1.8 g/day; $p < 0.05$) and L-FABP levels (28.0 vs 88.5 μg/g creatinine; $p < 0.05$).[93] Again, these changes were independent of effects on lipid parameters; no significant changes in serum levels of total cholesterol or triglycerides were seen.[93]

The addition of ezetimibe enhanced the effects of pitavastatin on markers of renal impairment in non-diabetic patients with stage I or II CKD.[81] Compared with pitavastatin monotherapy, pitavastatin plus ezetimibe produced significantly greater reductions in proteinuria (from 1512 to 1042 mg/day with pitavastatin alone and from 1508 to 786 mg/day with pitavastatin plus ezetimibe; $p < 0.01$ compared with pitavastatin treatment alone) and urinary L-FABP levels (from 57.8 to 34.4 μg/g creatinine with pitavastatin alone and from 57.6 to 29.4 μg/g creatinine with pitavastatin plus ezetimibe; $p < 0.01$ compared with pitavastatin treatment alone), although no significant changes in serum creatinine or GFR were reported in either group.[81] Multiple stepwise regression analysis showed that LDL cholesterol levels and urinary excretion of L-FABP and 8-OHdG were independently related to proteinuria (with β regression coefficients of 0.185 [$p < 0.001$], 0.312 [$p = 0.001$] and 0.557 [$p < 0.001$], respectively).[81]

Small improvements in renal function were seen in patients with CKD receiving pitavastatin in a subgroup analysis of the observational post-marketing LIVES study.[94] Patients with an estimated GFR <60 mL/min/1.73 m^2 ($n = 958$) experienced a significant increase in mean GFR from baseline to 104 weeks (47.8 vs 53.2 mL/min/1.73 m^2; $p < 0.001$). The presence/absence of proteinuria and change in serum HDL cholesterol level were identified in a multivariate analysis as factors predicting the increase in GFR.[94]

5. Tolerability

Pitavastatin was generally well tolerated in patients with hyperlipidemia with or without type 2 diabetes in studies of between 8 and 52 weeks' duration.[47-55] Treatment-related adverse events were generally mild to moderate in severity and occurred in 5.3–16.7% of patients receiving pitavastatin 2 or 4 mg daily[47,49-51] compared with 1.9–14.4% of patients receiving atorvastatin 10 or 20 mg daily[47,49] and 8.2–23.5% of patients receiving simvastatin 20 mg or 40 mg daily.[50,51] Figure 2 shows adverse events occurring with a frequency of ≥2% of patients treated with pitavastatin 1–4 mg/day in a pooled analysis of short-term controlled studies of up 12 weeks' duration.[10] Other adverse events occurring in >2% of patients in clinical trials include dizziness (2.9%), indigestion (2.2%), nasopharyngitis (2.7–3.2%), and headache (2.2–3.4%).[47,49,50]

Treatment discontinuation due to adverse events occurred in 0.7–4.2% of patients receiving pitavastatin.[47,49-51]

Laboratory parameters were closely monitored during trials of pitavastatin, but abnormalities were generally infrequent and not clinically significant. Elevated plasma creatine kinase (CK) level was the most commonly reported laboratory abnormality and occurred in 3.8–4.4% of patients.[49,51,52] Although clinical significance was reported in a heterogenous manner, the majority of studies reported no large and/or symptomatic increases in CK levels in patients receiving pitavastatin. Long-term follow-up of one study reported increased CK levels in 5.8% and myalgia/intercostal myalgia in 4.1% of patients after 52 weeks' treatment with pitavastatin 4 mg daily.[60] However, of the 55 patients experiencing myalgia, 34 patients were assessed as having mild and 21 as having moderate myalgia. Although elevated plasma CK level was reported in 12 of these patients, the CK level did not exceed ten times the upper limit of normal in any patient and there were no reports of rhabdomyolysis.[60] In the post-marketing LIVES study, 10.4% of patients developed adverse drug reactions, with the majority being mild in severity.[61] The only adverse event occurring in ≥2% of patients was an increase in CK levels (2.74%). Six of the 19 925 patients in the LIVES study evaluated for safety developed myopathy and only one patient developed rhabdomyolysis that fulfilled diagnostic criteria.[61] Elevated liver enzymes were reported in some patients receiving pitavastatin in several studies, but these elevations were generally mild and occurred in small numbers of patients.[49-54]

6. Discussion

Pitavastatin is a new addition to the statin family; it potently and consistently exerts favorable effects on lipid parameters,

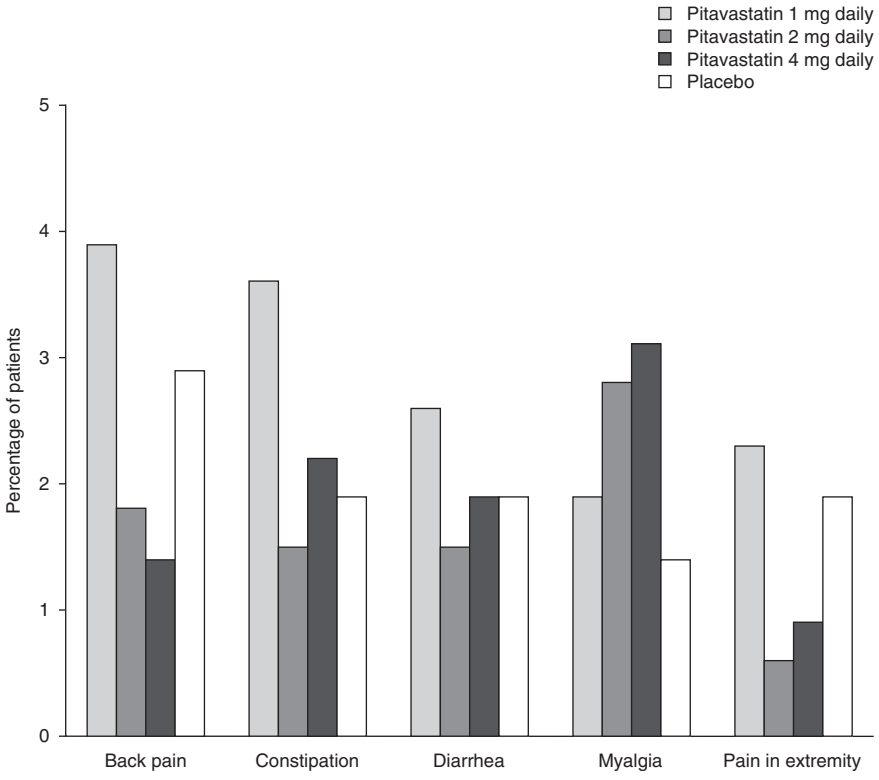

Fig. 2. Pooled results showing adverse events reported in ≥2% of patients and reported at a greater or equal rate than placebo in patients treated with pitavastatin 1, 2, or 4 mg daily or placebo in studies of up to 12 weeks' duration.[10]

produces additional effects independent of lipid reduction, is effective and well tolerated in patients with co-morbid conditions, and has a favorable pharmacokinetic profile.

After absorption, pitavastatin is taken up into the liver by OATP2 and undergoes minimal metabolism by CYP enzymes.[95,96] It, therefore, has a low propensity for drug-drug interactions with agents metabolized by CYP and grapefruit juice, a CYP3A4 substrate.[35,36,95,96] In contrast, atorvastatin, which is metabolized by CYP3A4, has an 83% greater exposure in the presence of grapefruit juice[35] and a high propensity for drug-drug interactions with other drugs metabolized by this CYP isoenzyme.[95] This is important in patients treated with statins that are likely to be receiving a number of other agents for the treatment of co-morbidities.

Pitavastatin 2 mg and 4 mg daily reduces elevated total cholesterol, LDL cholesterol, non-HDL cholesterol, and triglyceride levels from baseline in adult patients with primary hypercholesterolemia, including heterozygous familial hypercholesterolemia and mixed dyslipidemia, where the response to diet and other non-pharmacological measures is inadequate.[47-55] Reductions from baseline in total, LDL, and non-HDL cholesterol levels of 21–32%, 30–45%, and 35–41%, respectively, were seen in clinical trials, showing a potent lipid-lowering effect.[47-55] The proportion of patients achieving target LDL cholesterol levels reached as high as 94%. Potent reductions in the serum level of triglycerides of 10–30% were also seen. Pitavastatin was associated with a consistent trend towards increased serum HDL-cholesterol levels of between 2.6% and 6.2%, and in two studies this increase was statistically significant.[48,54] Pitavastatin was also associated with favorable effects on a number of other lipid parameters, including increases in levels of Apo AI and Apo AII and decreases in Apo B, Apo CII, Apo CIII, and Apo E levels.[47-55] Apo AI is an essential component of the HDL particle and pitavastatin promotes Apo AI production at lower concentrations than atorvastatin *in vitro*.[16] Moreover, pitavastatin is more potent than atorvastatin in stimulating lipoprotein lipase (LPL), which may also increase HDL levels.[97] The combination of a potent decrease in total and LDL cholesterol and increases in HDL cholesterol suggest that pitavastatin may produce substantial cardiovascular protection.

The favorable effects on lipid parameters of pitavastatin were at least as good as currently prescribed statins. Clinical trials show the lipid-lowering effects of pitavastatin to be similar to the potent agent atorvastatin.[47,49,53-55] Moreover, pitavastatin produced significantly greater improvements in lipid

profile than pravastatin and simvastatin in clinical trials.[50-52] Taken together, these results make pitavastatin an attractive therapeutic option in patients with primary hyperlipidemia or mixed dyslipidemia who have not responded to diet or other non-pharmacological measures.

Pitavastatin is effective in patients with type 2 diabetes or glucose intolerance and does not worsen markers of glucose intolerance, such as fasting blood glucose levels or HbA_{1c}. In diabetic patients, pitavastatin produced reductions in the levels of total, LDL, and non-HDL cholesterol of 12–27%, 18–41%, and 31%, respectively.[70-78] In addition, 6–29% reductions in serum triglyceride levels were seen.[71,73-78] Pitavastatin produced significantly greater reductions in LDL cholesterol levels versus atorvastatin in a small subset of patients with metabolic syndrome in one study.[54] The mechanism by which pitavastatin demonstrated a better improvement in lipid parameters compared with atorvastatin is unclear. LPL expression in 3T3-L1 preadipocytes is increased by pitavastatin *in vitro*.[97] LPL activity is often suppressed in the presence of insulin resistance but is crucial in very low-density lipoprotein and remnant lipoprotein metabolism.[98] Pitavastatin also produced favorable lipid responses in elderly patients[80] and in a small study in patients with CKD.[80] These attributes make pitavastatin a potential alternative to other statins in the treatment of patients with hyperlipidemia and metabolic co-morbidities.

Pitavastatin exerts a number of beneficial effects independent of lipid lowering. The JAPAN-ACS study provided good evidence that pitavastatin improves atherosclerosis and showed that it was non-inferior to atorvastatin at reducing plaque volume in patients with ACS undergoing PCI.[84] A number of small studies have demonstrated favorable effects with pitavastatin, including beneficial effects on cardiovascular function,[67-69,88,90-92] and reductions of markers of CKD.[81,89,93] A number of exploratory analyses have shown pitavastatin to be associated with reductions in serum levels of markers of inflammation and oxidative stress, suggesting that the agent may have beneficial effects on the inflammatory changes occurring in the arterial wall.[48-50,59,60,65,66,68,72,73,81,84,86-89] Taken together, these results suggest that, in addition to contributing to a reduction in atherosclerosis, pitavastatin may have beneficial effects on cardiovascular risk in patients with hyperlipidemia with or without co-morbid metabolic conditions.

Pitavastatin is generally well tolerated and the majority of adverse events are mild to moderate in severity.[47-55] Like most statins, pitavastatin has been associated with rare cases of myopathy and rhabdomyolysis, and these have been the focus of safety analyses in clinical trials and post-marketing surveillance studies. While an elevated plasma CK level was seen in up to 5% of patients treated with pitavastatin,[49,51,52] the number of cases of myopathy or rhabdomyolysis fulfilling diagnostic criteria was extremely low.[61]

The majority of clinical studies were in Asian populations and clinical data in European populations and other ethnic groups are lacking. Application of these study results to a more heterogenous population in Europe or the US should, therefore, be done with caution until further studies are available.

7. Conclusion

Pitavastatin potently and consistently reduced the levels of total cholesterol and LDL cholesterol in clinical trials, and was consistently associated with a trend towards increased HDL cholesterol levels. These favorable effects on lipid parameters are generally similar to those observed with atorvastatin and tend to be somewhat greater than the other statins, such as simvastatin. These benefits are also evident in special patient populations, such as patients with type 2 diabetes, CKD, and the elderly.

Aside from its beneficial effects on lipid profiles, pitavastatin may have additional favorable effects that are independent of its cholesterol-lowering properties and may contribute towards decreasing patients' risk of cardiovascular morbidity and mortality. These effects include regression of atherosclerosis, improved cardiovascular and endothelial function, and reduced levels of inflammatory markers, such as hs-CRP.

Pitavastatin demonstrates good tolerability in clinical trials and in a large post-marketing surveillance study, has little deleterious effect on glucose tolerance, and exhibits a low incidence of musculoskeletal adverse events.

Pitavastatin has a favorable pharmacokinetic profile. It is less likely to interact with drugs metabolized by CYP enzymes and this is particularly important in patients with multiple pathologies, such as type 2 diabetes and cardiovascular and renal disease, who often require polypharmacy. Future studies are needed to reconfirm the efficacy of pitavastatin in non-Asian populations and to define the effects of pitavastatin on reducing mortality and morbidity in patients at high risk of cardiovascular events.

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